

42 sub 51
Claim 32 (amended) A conjugate of claim 29 wherein the carbohydrate moiety is a galactosyl residue and is substituted with a glycosyl residue.

RECEIVED

MAY 14 2001

TECH CENTER 1600/2900

REMARKS

Reconsideration of this application is requested in view of the amendments to the claims and the remarks presented herein.

The claims in the application are claims 29 to 32, 35, 38 to 40, 42 to 44, 46 and 47, all other claims having been cancelled. Claims 29 and 33 have been combined and therefore, claim 33 is cancelled. Claims 34, 36, 37, 41 and 45 now read on embodiments no longer encompassed by claim 29 and have therefore been cancelled. The claimed invention has now been restricted to a carbohydrate peptide conjugate for which group B is a tumor antigen.

Claims 29 to 47 were rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification sufficiently. The Examiner was of the opinion that the specification did not provide support for the structures wherein the middle Lys residue has 9 to 13 residues as defined in the small variables n and m. The Examiner is of the opinion that the specification fails to provide a description wherein the Lys contains more than three residues as given in the figures and there is no teaching of how more than three Lys residues are linked

together to form the Lys bridge.

Applicants respectfully traverse this ground of rejection since the amended claims are properly supported in the specification as filed. Claim 29 as presented is clearly supported by the specification. Figure 1 of the text as filed disclosed a general structure of the four carbohydrate peptide conjugates of claim 29. It is agreed that Figure 1 does not disclose the middle Lys residue as being 9 to 13 residues as defined by the variables of n and m. However, lines 19 to 22 of page 7 of the application state that a conjugate encompassed by the invention "comprises at least 3 lysine and up to 15 lysine residues covalently linked to one another." Starting from the conjugates disclosed in Figure 1 and reading the structures in light of the specification, one skilled in the art would have been able to draw the conjugate structures defined in claim 29.

For the two structures B4-T4-M and B2-T2-M, there is but one way to include the variable number of lysine residues in the structure which is to have the single polymeric lysine chain of a variable length wherein the length range is disclosed in line 21 of page 7 of the application. With regard to the structures of B8-T-M and B4-T4-M, the single basic change that is available to one skilled in the art when combining Fig. 1 and lines 19 to 22 of page 7 of the specification is also to make the length of the central lysine polymeric chain variable with the length range being defined

in line 21 of page 7. Therefore, the conjugate structures as claimed were clearly disclosed in the text as filed and withdrawal of this ground of rejection is requested.

All of the claims were rejected under 35 USC 112, second paragraph, as being indefinite for the reasons set forth in paragraphs A to D.

Applicants respectfully traverse this ground of rejection since it is deemed that the present claim 29 is now definite. Claim 29 has been combined with claim 33 and claim 33 has been cancelled. The expression "comprising a dendrimeric poly-lysine carrier enabling multiple epitopes to be covalently attached thereto wherein said carbohydrate peptide conjugate is" has been added which serves as a basis for the end of the claim. The definition of group B has been modified to limit the scope of the claim to conjugates wherein the carbohydrate moiety is restricted to a tumor antigen. Claim 32 has been amended to replace the expression "by another" with the expression "with a". The claimed invention is now restricted to carbohydrate peptide conjugates for which group B is a tumor antigen. Therefore, the amended claims are believed to be definite and withdrawal of this ground of rejection is requested.

Claims 1 to 14 and 17 to 25 were rejected as not being patentably distinct from that of claims 1 to 14, 24 to 29 and 33 to

36 of the copending application Serial No. 09/405,986.

Applicants respectfully traverse this ground of rejection since the claims in the copending application are not directed to the same invention. Due to the fact that the Examiner had a 15-way restriction requirement in the copending application, claims 17 to 22 were elected which are drawn to a linear carbohydrate conjugate and is not conflicting with the claims of the present application which, as noted above, are drawn to a different invention. Therefore, withdrawal of this ground of rejection is requested.

All of the claims were rejected under 35 USC 102(a) as being anticipated by the Bay et al reference since the present application is entitled to the provisional application filing date of March 27, 1997 and it is deemed that this ground of rejection is obviated since the publication date of Bay et al is subsequent to Applicants' priority date. Therefore, this ground of rejection is moot.

Claims 29, 36, 37, 39 to 40 and 44 to 47 were rejected under 35 USC 102(a) as being anticipated by or under 35 USC 103 as being obvious over the Chong et al patent. Claims 29, 33, 36, 37, 40 and 44 to 47 were rejected under 35 USC 103 as being obvious over the Chong et al patent taken in view of the Zanni et al reference for reasons of record and claims 30 to 31 were rejected as being obvious over the Chong et al patent taken in view of the Zanni et al reference taken in further view of the Fung et al reference.

Claims 34 and 35 were rejected under 35 USC 103 as being obvious over the Chong et al patent taken in view of the Zanni et al and Fung et al references taken in further view of the Tam patents for reasons of record.

Applicants respectfully traverse these grounds of rejection since none of the prior art references cited by the Examiner or any combination thereof disclose a carbohydrate peptide conjugate having a carbohydrate moiety which is a tumor antigen as now claimed in claim 29. Therefore, the claimed carbohydrate peptide conjugate is clearly novel over each of the prior art references.

The Chong et al patent discloses MAG constructs wherein a carbohydrate moiety is a bacterial antigen derived from Hemophilus influenzae. The production of an immune response against the bacterial antigen cannot predict that any MAG construct would also be efficient for stimulating an immune response against a tumor antigen. The Chamberlain et al article, Drugs, Vol. 57, (3), pages 309-325 enclosed herewith for the Examiner's convenience, relates to anti-cancer vaccines and on page 312, section 2.2 of this article, it is clearly stated that "Antibody responses against carbohydrate antigens on the surface of encapsulated organisms such as...and Hemophilus influenzae as above can provide protective immunity. Similar antigens on human cancers are also potential targets for immune recognition but rarely induce responses in vaccine protocols using whole tumor or tumor lysate strategies."

Therefore, it is clear to one skilled in the art having the knowledge of Chong et al would not have used the MAG constructs disclosed by Chong et al to raise an immune response against tumor antigens.

Applicants are submitting a copy of an article by Pardoll (Clinical Immunology, Vol. 95, No. 1, pp.44-62) which explains why technical means which are useful to raise an immune response against various viral, bacterial or fungal antigens is not a priori efficient for inducing an immune response against a tumor antigen. On page 44, it is stated that to induce an immune response against tumor associated antigens, one skilled in the art must overcome a situation of immunological tolerance of the immune system with respect to tumor antigens which is not the case with the antigens produced by invading pathogens. Pardoll states that "Therapeutic vaccines for cancer of any type must overcome this tolerance state of the immune system in order to activate clinically immune responses." The necessity to overcome immune tolerance to raise an efficient immune response is not disclosed by Chong et al, the Zanni or Tam references which do not even mention tumor antigens. Moreover, Chong et al only discloses a conjugate between KLH and a tumor antigen which is active only when administered with immunological adjuvant whereas the claimed conjugates are active even without adjuvant as can be seen from the examples.

Applicants are submitting herewith a copy of a review by

Schreiber (Fundamental Immunology, fourth edition, chapter 37, pp. 1237-1262) which relates to tumor immunology. Pages 1256 and 1257 under the headings "Tolerance Versus Ignorance", the authors underline the specific immuno-tolerant situation which is encountered when an anti-tumor immune response is desired which tolerance is not encountered for the induction of immune responses against pathogenic antigens. Applicants are also submitting herewith an article by Dalglish (British Journal of Cancer, vol. 82, (10) pp. 1619-1624) which relates to cancer vaccines. On page 1620, the last full paragraph of the right hand column, the authors clearly technically distinguished between immune responses raised against pathogens, i.e. bacterial antigens and immune responses against tumor antigens. On page 1621, right column, the numerous problems which are encountered when an anti-tumor immune response is desired are listed and these problems are not encountered for viral, bacterial or fungal agents. Dalglish further supports the inventors' statement according to which the teachings of Chong et al or any prior art reference cited by the Examiner could not be transposed by one skilled in the art to the area of anti-tumor vaccines.

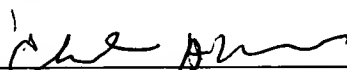
In conclusion, it flows from the preceding analysis that one skilled in the art had no incentive to use the constructs disclosed in any of the prior art references cited by the Examiner to induce an anti-tumor immunity. Moreover, since the physiological mechanisms of an immune response against the pathogen and an immune

response against a tumor associated antigen are radically distinct and one skilled in the art would not have been motivated to combine the teachings of the references as the Examiner has done with the benefit of Applicants' disclosure. Therefore, the claimed peptide conjugates are clearly non-obvious and patentable. Therefore, withdrawal of these grounds of rejection is requested.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
Bierman, Muserlian and Lucas

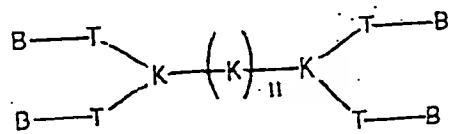
By:


Charles A. Muserlian #19,683
Attorney for Applicants
Tel.# (212) 661-8000

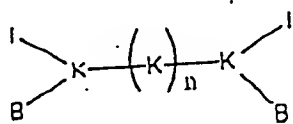
CAM:ds
Enclosures

comprising a dendrimeric poly-Lysine ^{carrier} enabling multiple epitopes to be covalently attached thereto, wherein said carbohydrate peptide conjugate is

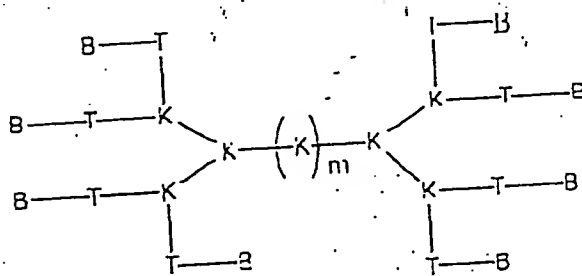
29. A carbohydrate peptide conjugate selected from the group consisting of the conjugates of the following formulae



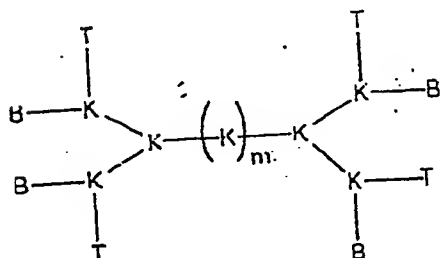
(B4-T4-M)



(B2-T2-M)



(B8-T8-M)



(B4-T4-M)

wherein:

which is a tumor antigen

- B denotes a structurally defined carbohydrate moiety, or a derivative thereof, containing B epitope other than a sialoside, or several identical or different B epitopes;

- T denotes a peptide comprising one T epitope or several identical or different T-epitopes;

- K denotes a lysine residue;

- n is an integer from 1 to 13;

- m is an integer from 1 to 9; and

wherein the B and T groups are covalently attached to the poly-lysine carrier.

RECEIVED

MAY 14 2001

TECH CENTER 1600/2900

30. A conjugate of claim 29 wherein the carbohydrate moiety is galactosyl.

31. A conjugate of claim 29 which comprises 3 lysine residues, at least 4 T cell epitopes, which may be the same or different, linked to the NH₂ ends of 2 of the lysine residues and 4 α -galactosyl-N-acetyl-Serine residues.

32. A conjugate of claim 29 wherein the carbohydrate moiety is a galactosyl residue and is substituted ^{with a} ~~by another~~ glycosyl residue.

33. A conjugate of claim 29 wherein the carbohydrate is a tumor antigen.

34
145 A conjugate of claim 29 wherein the epitope T is the 103-
peptide of the VP1 protein of poliovirus type 1.

35. A conjugate of claim 29 wherein the carbohydrate is grafted in combination with a tumor peptide CD8⁺ T cell epitope.

36. A conjugate of claim 29 wherein the carbohydrate is of bacterial or fungal origin.

37. A conjugate of claim 29 wherein the carbohydrate is from capsular bacterial polysaccharides selected from the group consisting of *Neisseria meningitidis*, *Haemophilus influenza*, *Streptococcus pneumonia* and other *Streptococcus* species other than sialylated polysaccharides.

38. A conjugate of claim 29 wherein the carbohydrate is selected from the group consisting of Tn antigen, di-Tn antigen, Tri-Tn antigen, T^{*} antigen and hexa-Tn antigen.

39. A pharmaceutical composition comprising the conjugate of claim 29 and a suitable carrier and adjuvant.

40. A vaccine comprising the conjugate of claim 29.

41. An immunogenic composition comprising at least one carbohydrate peptide conjugate of claim 29 capable to elect an

~~immune response against a viral infection caused by a pathogen.~~

42. An immunogenic composition comprising at least one carbohydrate peptide conjugate of claim 29 wherein said composition is capable of increasing the survival of a tumor bearing human or animal.

43. An immunogenic composition comprising at least one carbohydrate peptide conjugate of claim 42 wherein said conjugate comprises different carbohydrate antigens to induce more efficient anti-tumor immunity against cancers.

44. A method of inducing an immune response to at least one member of the group consisting of B-cells and T-cells in a human or animal body, wherein the conjugate of claim 29 is administered to said human or animal body.

~~45. A method for inducing an immune response to at least one member of the group consisting of B-cells and T-cells in a human or animal body against bacteria wherein the conjugate of claim 36 is administered to said human or animal body.~~

46. A method for inducing a B-cell response in a human or animal body, wherein the conjugate of claim 29 is administered to said human or animal body.

47. A method of vaccination of a human or animal body wherein the conjugate of claim 29 is administered to said human or animal body.--

REMARKS

Reconsideration of this application is requested in view of the amendments to the specification and claims and the remarks presented herein.

The claims in the application are claims 29 to 47, all other claims having been cancelled. In addition, page 35 has been cancelled and a new Abstract of the Disclosure has been provided as required by the MPEP. It is requested that the formal drawings request be held in abeyance until there is an indication of allowable subject matter.

The disclosure was objected to as having no sequence identification number for the sequence set forth in lines 22 and 26 of page 28 and for not capitalizing the trademark on page 21.

Applicants respectfully request withdrawal of these grounds of objection. There is no sequence identification number on page 28 since the same sequence is a known sequence and is not part of Applicants' invention. The trademark Tween has been capitalized where appropriate and the expressions in claims 22 and 23 objected